Aktuelle internistische Therapieoptionen bei Weichteilsarkomen

U. Kreibich

Klinik für Innere Medizin III

Heinrich-Braun-Klinikum Zwickau gGmbH

CTx Weichteilsarkome - Agenda

- Allgemeines
- Therapie palliativ
- Ausblick palliative Therapie
- Therapie neoadjuvant/adjuvant

Weichteilsarkome - Allgemeines

- Inzidenz: ca 1–2/100 000/Jahr Deutschland, 4-5/100000 in Europa

- mehr als 50 Subtypen:

Leiomyosarkome	15-25 %
Liposarkome	10-15 %
Pleomorphe Sarkome / NOS (früher MFH)	15-25 %
Synovialsarkome	6-10 %
Angiosarkome	1 %
andere	< 1-5 %

CTx Weichteilsarkome - Agenda

Allgemeines

- Therapie palliativ

Ausblick palliative Therapie

- Therapie neoadjuvant/adjuvant

Royal Marsden between 1991-2010

Metastatic soft tissue sarcoma: an analysis of systemic therapy and impact on survival Harris S *et al* Abs. 10545

OS has improved over last 20 years to ca. 18 months

Figure 4: Trends in Survival with Treatment

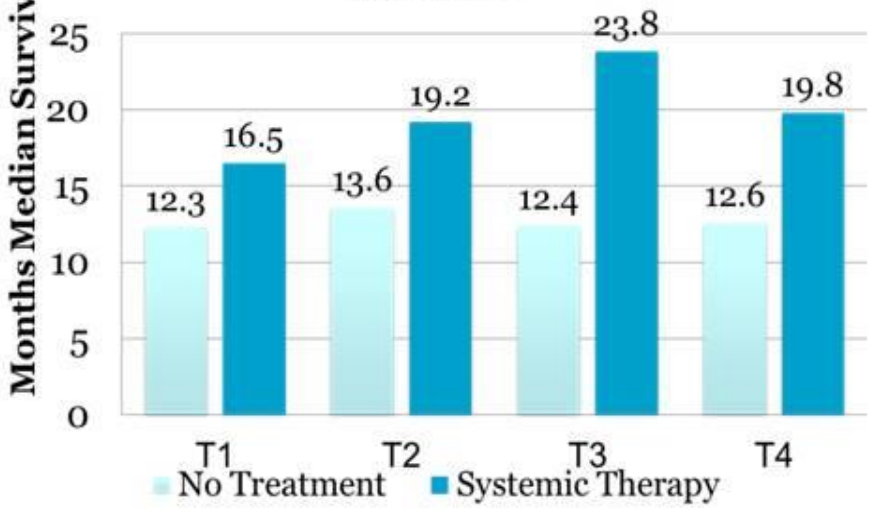
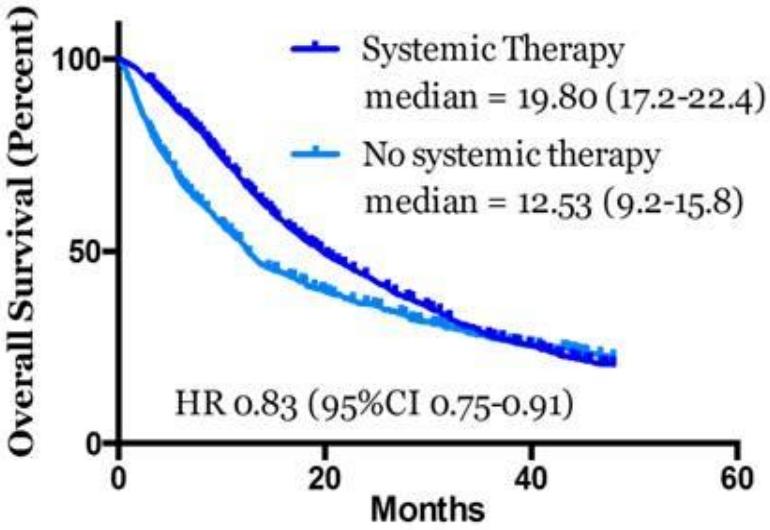


Figure 2: Systemic Therapy and Survival



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Metast. WTS- Erstlinientherapie

- **Doxorubicin mono ist weiter Standard**

- **Kombination Anthrazyklin/Ifosfamid individuell,**
  höhere Ansprechraten, mehr Tox., PFS-Vorteil, kein signif. OS-Benefit

Therapie (fortgeschr. +metast WTS)- Esmo-Guidelines 2014:
Standard chemotherapy is based on anthracyclines as the **first-line** treatment [I, A] As of today, there is no formal demonstration that multiagent chemotherapy is superior to single-agent chemotherapy with doxorubicin alone in terms of overall survival (OS). However, a higher response rate can be expected, in particular… Therefore, multiagent chemotherapy with adequate-dose anthracyclines plus ifosfamide may be the treatment of choice, particularly when a tumour response is felt to be potentially advantageous and patient performance status is good…

PFS significantly improved but not OS

(intention to treat analysis)

OS

PFS

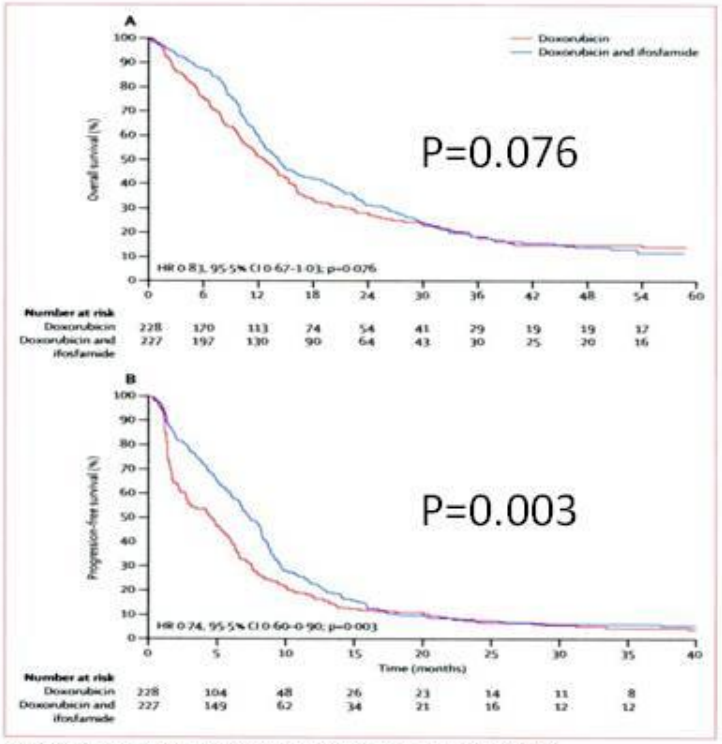

Figure 2: Kaplan-Meier curves for overall survival (A) and progression-free survival (B)
HR=hazard ratio.

Judson et al Lancet Oncol 2014;15(14):415-23

Median overall survival:
Doxorubicin: 12.8 mths
Doxorubicin + ifosfamide: 14.3 mths
1.5 month increase in median OS

Median PFS
Doxorubicin: **4.6 mths**
Doxorubicin + ifosfamide: **7.4 mths**

Overall response rate:
Doxorubicin: **13.6%**
Doxorubicin + ifosfamide: **26.5%**

NCRI National Cancer Research Institute

SAKK

GeDDiS

A prospective randomised controlled phase III trial of gemcitabine and docetaxel compared with doxorubicin as first line treatment in previously untreated advanced unresectable or metastatic soft tissue sarcoma

Beatrice Seddon, Jeremy Whelan, Michael Leahy, Penella Woll, Fiona Cowie, Christian Rothermundt, Zoe Wood, Sharon Forsyth, Paul Patterson, Stephen Nash, Sandy Beare

CANCER RESEARCH UK

Cancer Research UK and UCL Cancer Trials Centre

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Presented By Beatrice Seddon at 2015 ASCO Annual Meeting

Patient characteristics

		Dox (N=129) N (%)	GemDoc (N=128) N (%)
Sex	Male	50 (38.8)	51 (39.8)
	Female	79 (61.2)	77 (60.2)
Age (yrs)	median (range)	56 (18.7-82.2)	55 (21.1-75.4)
Weight (Kg)	median (range)	77.0 (42.7-159.0)	77.7 (43.6-130.0)
WHO PS	0	55 (42.6)	52 (40.6)
	1	63 (48.8)	67 (52.3)
	2	11 (8.5)	9 (7.0)
Histology	Uterine leiomyosarcoma	36 (27.9)	35 (27.3)
	Synovial sarcoma	5 (3.9)	6 (4.7)
	Pleomorphic sarcoma	16 (12.4)	16 (12.5)
	Other eligible sarcomas	72 (55.8)	71 (55.5)

Trial Design

Eligible patients (n=250)

***Stratification factors:**

- age (≤18 years, >18 years)
- histological subtype:
  - Uterine leiomyosarcoma
  - Synovial sarcoma
  - Pleomorphic
  - Other types of eligible STS

1:1 randomisation*

Control Arm:
Doxorubicin 75 mg/m^2 day 1
every 21 days x 6 cycles

Investigational Arm:
Gemcitabine 675 mg/m^2 days 1, 8
Docetaxel 75 mg/m^2 day 8
every 21 days x 6 cycles

Disease assessments (RECIST 1.1) at:

- Baseline
- 12 weeks post randomisation
- 24 weeks post randomisation
- 12 weekly thereafter

Quality of life assessments at:

- Baseline
- 12 weeks post randomisation
- 18 weeks post randomisation
- 24 weeks post-randomisation

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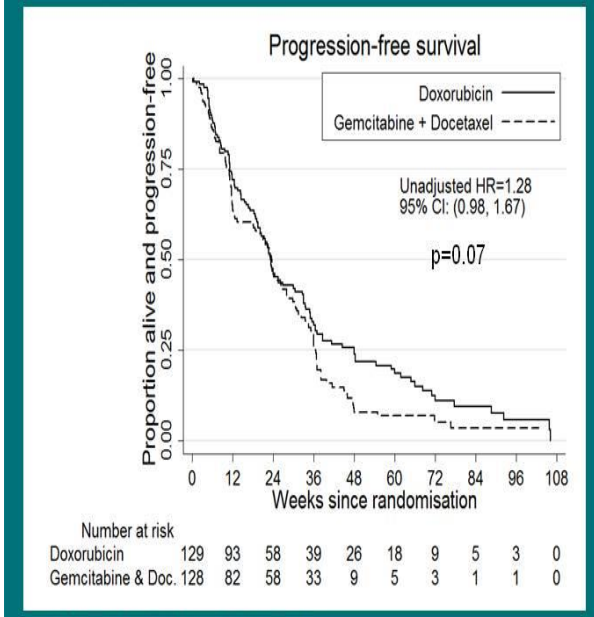
GeDDiS trial Endpoints

- Primary endpoint:
  - Proportion of patients alive and progression free at 24 weeks after randomization
- Secondary endpoints:
  - Proportion of patients alive and progression free at 12 weeks after randomization
  - Median progression-free survival
  - Overall survival
  - Adverse events (NCI CTCAE v4.03)

GeDISS- Ergebnisse

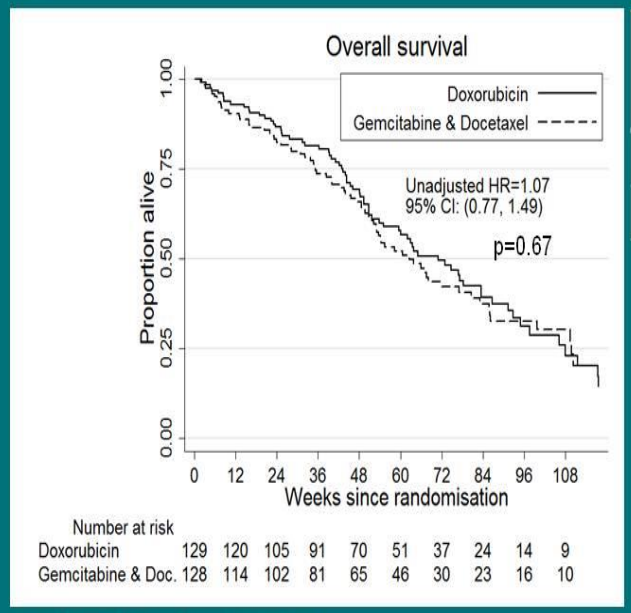
- Kein Unterschied in PFS und OS
- Gem/Doce mit mehr tox-bedingten Therapieabbrüchen

Progression-free survival



	Median PFS (months)	24 week PFS
Dox	5.4	46.1%
GemDoc	5.5	46.0%

Overall survival



	Median OS (mths)	24 week OS
Dox	16.4	86.7%
GemDoc	14.5	82.5%

Modif. , Presented By Beatrice Seddon at 2015 ASCO Annual Meeting

Compliance to trial treatment

Reason	Dox (N=129)	GemDoc (N=128)
Total withdrawals during treatment	60 (47%)	80 (63%)
Disease progression	34 (57%)	39 (49%)
Symptomatic deterioration	4 (7%)	3 (4%)
Unacceptable toxicity	1 (2%)	13 (16%)
Serious adverse event	2 (3%)	2 (3%)
Death	5 (8%)	4 (5%)
Other	14 (23%)	19 (11%)

Zweitlinientherapie

- **Kein Standard-Schema**

Zugelassene Medikamente:
Doxorubicin, Epirubicin, Ifosfamid, DTIC;
Trabectedin (2nd line),
Pazopanib (ab 2nd line, nicht für Liposarkom),

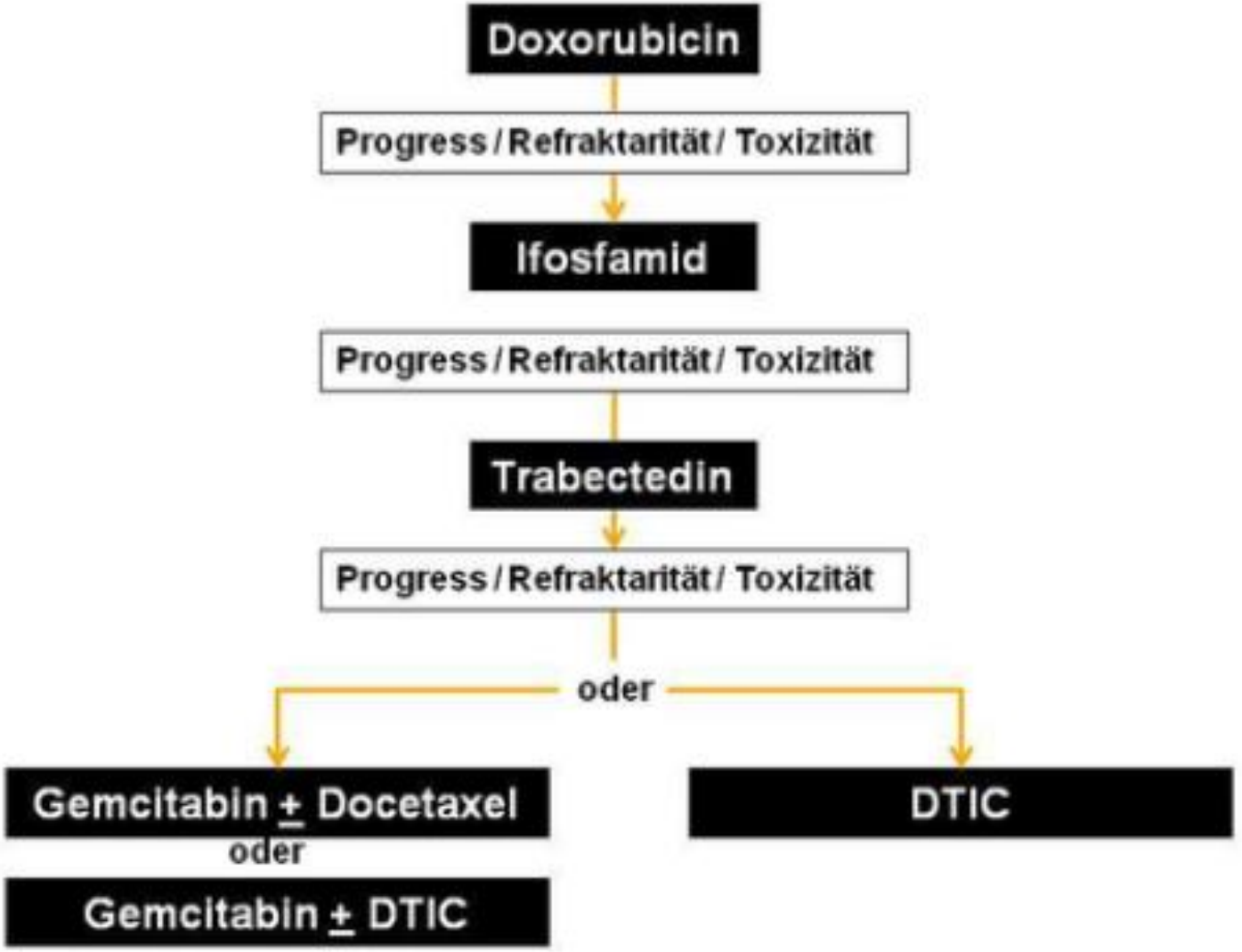
Weitere etablierte Substanzen:
Gemcitabin+/-Docetaxel, Paclitaxel

„subgruppenspezifische“ Therapie

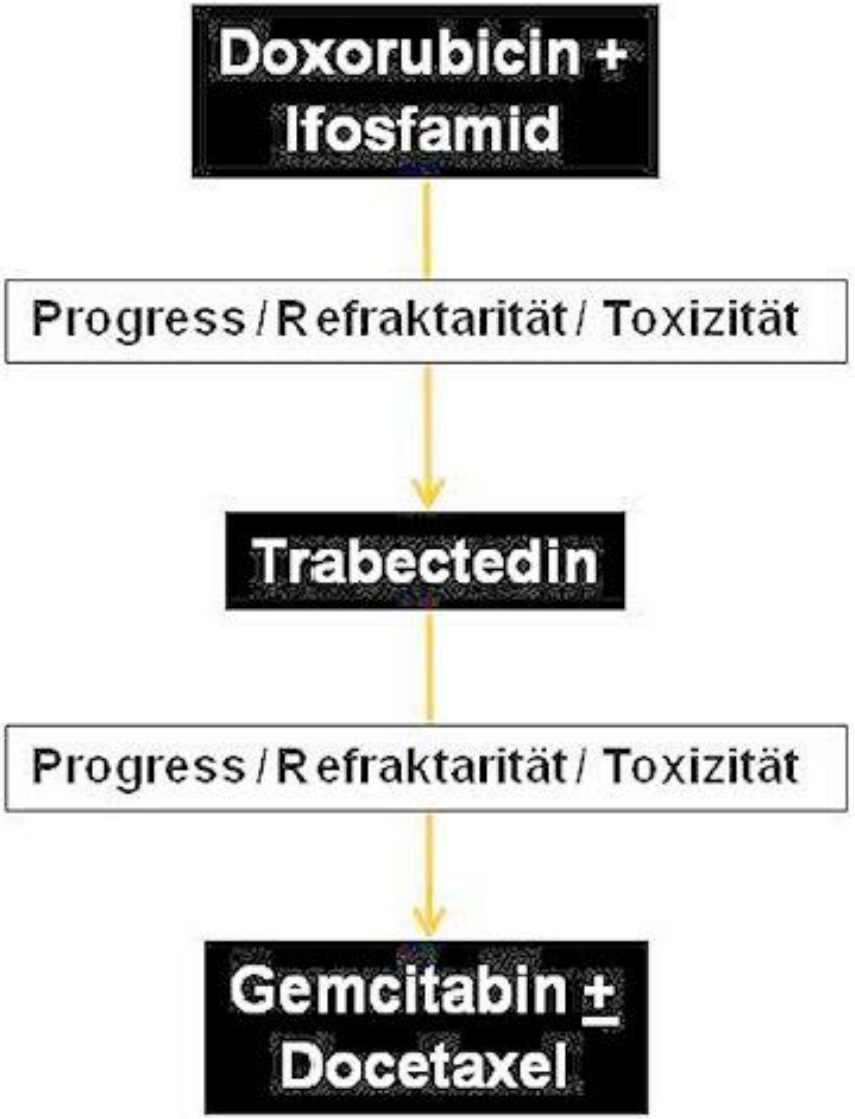
Tumortyp	Eventuelle Therapieoptionen1
Synovialsarkom	Ifosfamid + Adriamycin, Trabectedin
Liposarkom	Adriamycin, Ifosfamid, Trabectedin, Gemcitabin ± Docetaxel, DTIC
Leiomyosarkome	Adriamycin, Ifosfamid, Gemcitabin ± Docetaxel, Trabectedin, DTIC
uterine Leiomyosarkome	Adriamycin (±DTIC / ±Ifosfamid), Gemcitabin ÷ Docetaxel, Ifosfamid, Trabectedin
Endometriale Stromasarkome (low-grade)	Aromataseinhibitoren, Gestagene, GnRH-Analoga
Gastrointestinale Stromatumoren	Imatinib, Sunitinib
Dermatofibrosarcoma protuberans (t: 17;12)	Imatinib
Desmoide	NSAID, Tamoxifen, Interferon, (lipos.) Adriamycin, Vinca-Alkaloide., Methotrexat, Imatinib, Sorafenib
Angiosarkome (Haut/Kopf)	Adriamycin, Paclitaxel, Gemcitabin ± Taxan, Vinorelbin, Sorafenib, Bevacizumab[x]
Non-Lipo/Non-LMS (MFH; pleomorphe, undifferenzierte Sarkome, NOS, etc)	Adriamycin+Ifosfamid, Gemcitabin ± Docetaxel, Trabectedin, Sorafenib?[x]
Rhabdomyosarkome	Adriamycin/Actinomycin-D, Oxazophosphorine, Vincristin, Topoisomerase-I-Inhibitoren
Alveolarzellsarkom	Sunitinib[x] , Cediranib[x]
MPNST	Adriamycin, Ifosfamid, Gemcitabin±Vinorelbin, Sorafenib[x], platinhaltige Kombinationen
Solitärer fibröser Tumor	Temozolomid+Bevacizumab, Sunitinib, Adriamycin, Ifosfamid
Tenosynovialer Riesenzelltumor/Pigmentierte villonoduläre Synovitis	Imatinib
Chordome	Imatinib, Sunitinib[x], Erlotinib[x]

Beispiel Therapiealgorithmus Liposarkome

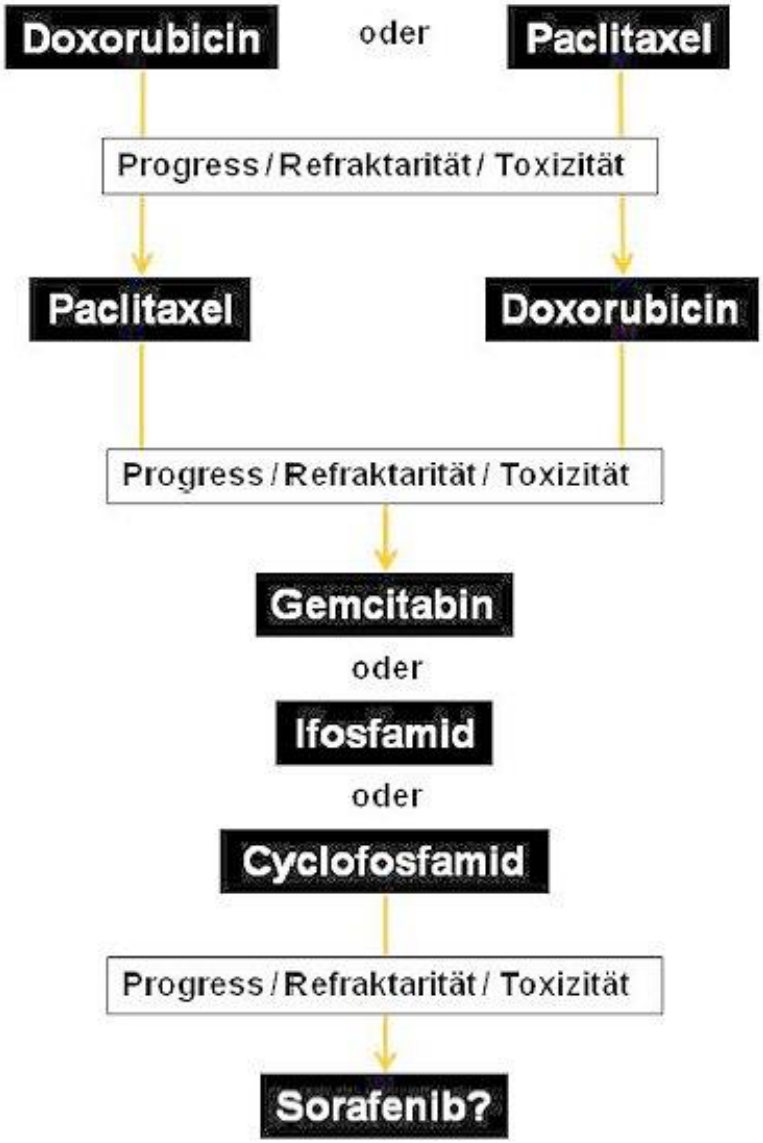
nach Leitlinie DGHO

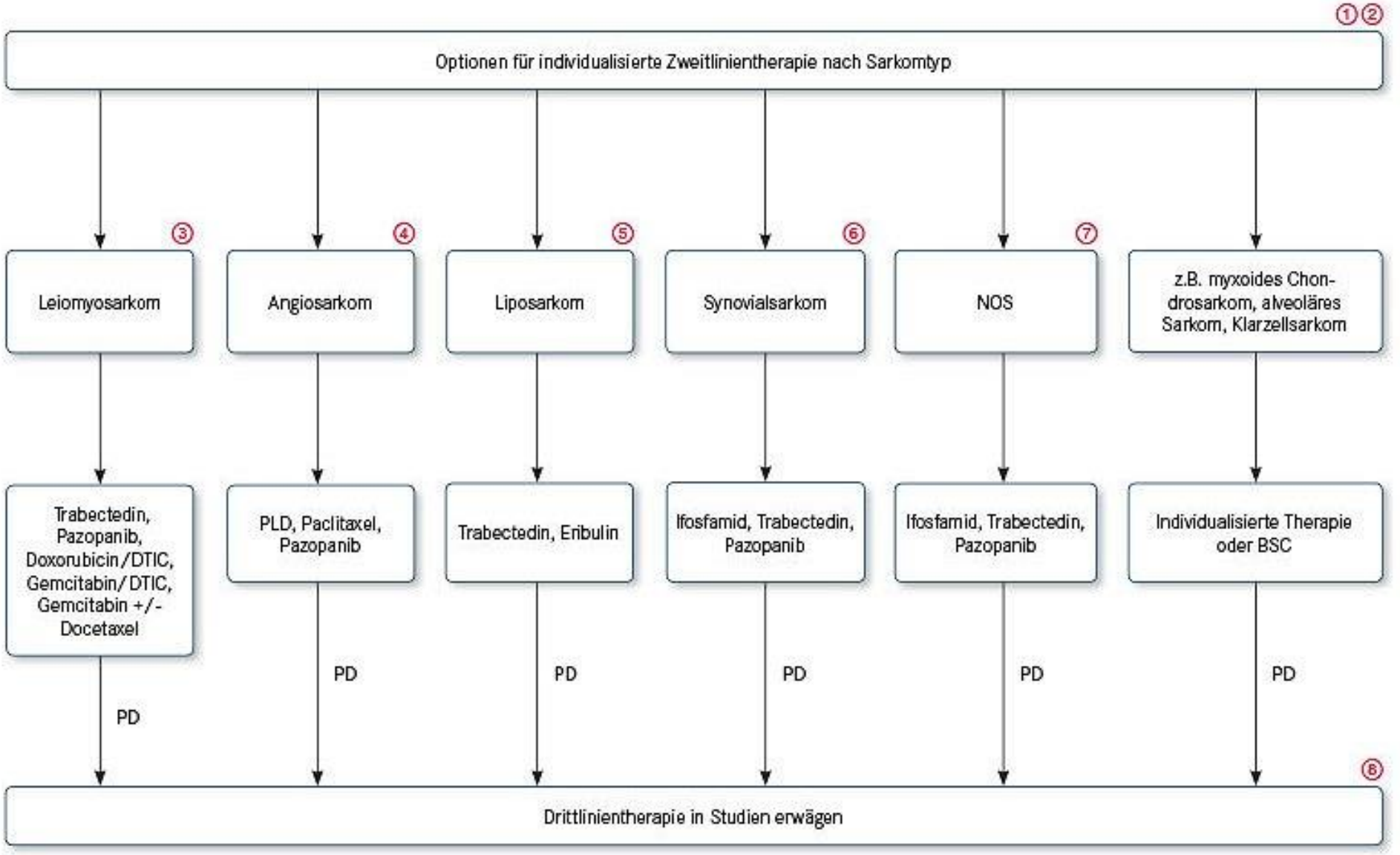


Synovialsarkome - möglicher Therapiealgorithmus



Angiosarkome - möglicher Therapiealgorithmus




①②
Optionen für individualisierte Zweitlinientherapie nach Sarkomtyp
③
Leiomyosarkom
④
Angiosarkom
⑤
Liposarkom
⑥
Synovialsarkom
⑦
NOS
z.B. myxoides Chondrosarkom, alveoläres Sarkom, Klarzellsarkom
Trabectedin, Pazopanib, Doxorubicin/DTIC, Gemcitabin/DTIC, Gemcitabin +/- Docetaxel
PLD, Paclitaxel, Pazopanib
Trabectedin, Eribulin
Ifosfamid, Trabectedin, Pazopanib
Ifosfamid, Trabectedin, Pazopanib
Individualisierte Therapie oder BSC
PD
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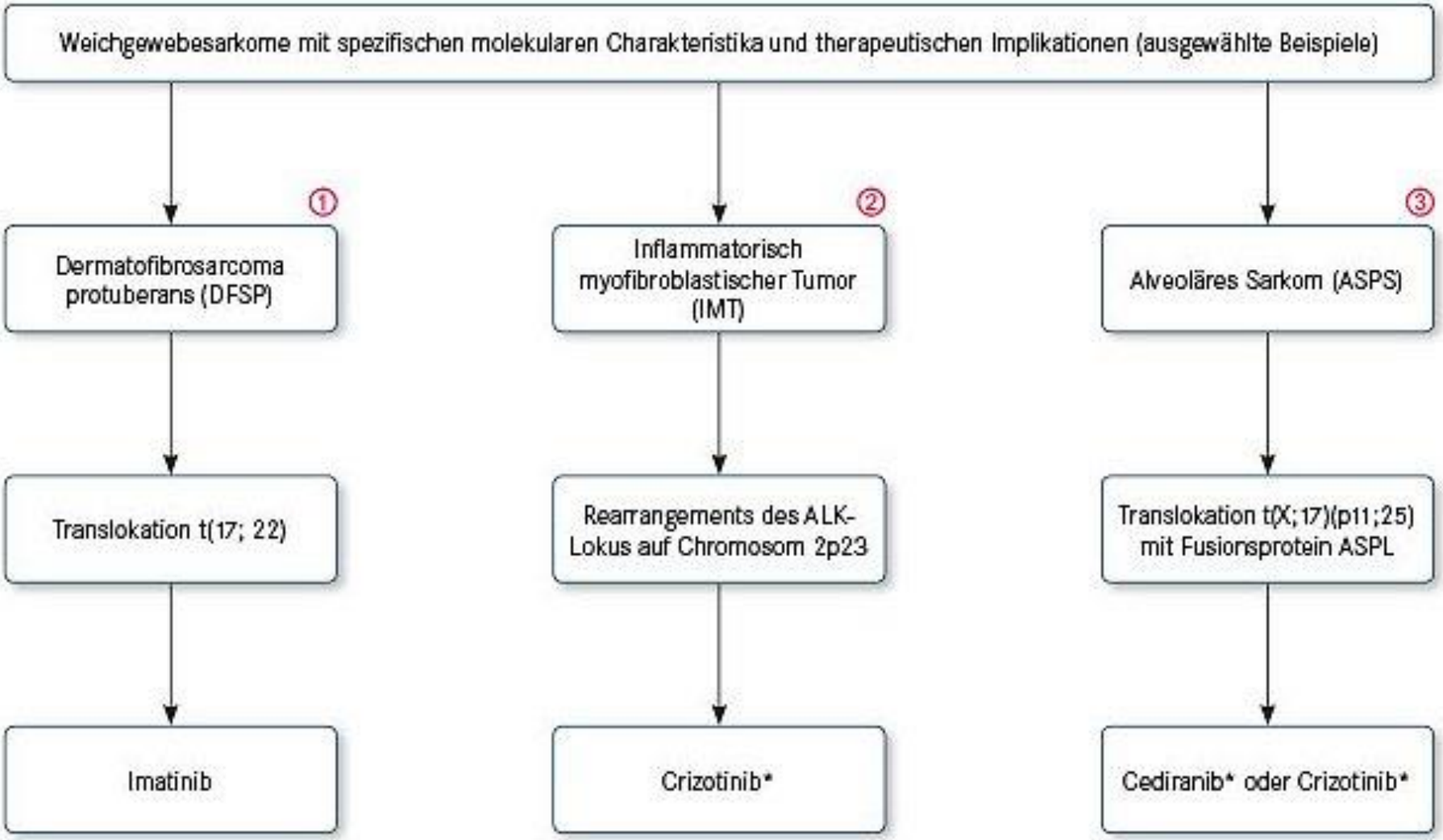
⑧
Drittlinientherapie in Studien erwägen



* experimenteller Ansatz

CTx Weichteilsarkome - Agenda

Allgemeines

Therapie palliativ

- Ausblick palliative Therapie

Therapie neoadjuvant/adjuvant

Randomized, open-label, multicenter, phase 3 study of eribulin versus dacarbazine in patients (pts) with leiomyosarcoma (LMS) and adipocytic sarcoma (ADI)

Patrick Schöffski, MD, MPH
Department of General Medical Oncology
University Hospitals Leuven, Leuven Cancer Institute
KU Leuven, Leuven, Belgium

Abstract # LBA10502 submitted by **P Schöffski**, R Maki, A Italiano, H Gelderblom, E Choy, G Grignani, V Camargo, S Bauer, SY Rha, S Chawla, JY Blay, P Hohenberger, DR D'Adamo, B Wang, B Chmielowski, A LeCesne, GD Demetri, and S Patel. Clinicaltrials.gov identifier: NCT01327885.

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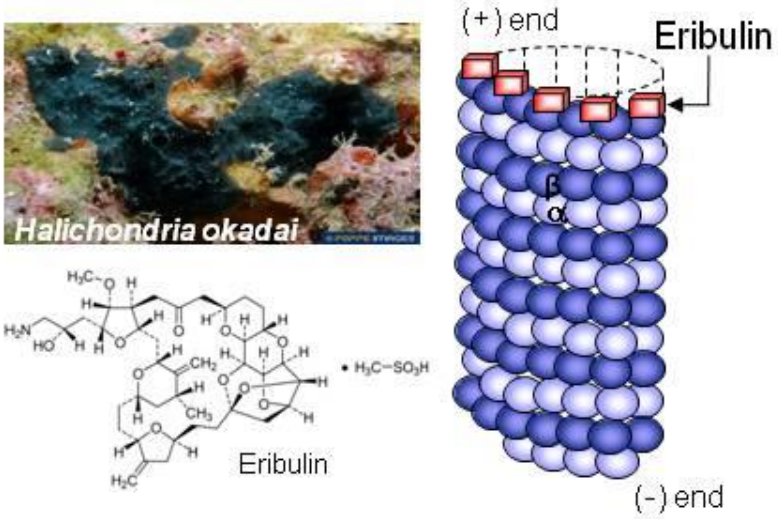
LBA10502: Randomized, open-label, multicenter, phase III study of eribulin versus dacarbazine in patients (pts) with leiomyosarcoma (LMS) and adipocytic sarcoma (ADI) - Patrick Schöffski et al

Eribulin: a novel microtubule dynamics inhibitor

- Eribulin is a fully synthetic, optimized analog of the marine sponge natural product halichondrin B[1]
- Approved in 59 countries as third- (USA), second- (EU), or first-line (Japan) monotherapy for patients with advanced/metastatic breast cancer[4,5]
- In preclinical models:
  - Eribulin primarily has antimitotic effects based on a novel mode of inhibiting microtubule dynamics[1,2]
  - Eribulin also exerts other complex effects on tumor biology, including vascular remodeling, reversal of epithelial-mesenchymal transition, and suppression of migration and invasion[6,7]

Eribulin has a distinct mode of action[2,3]



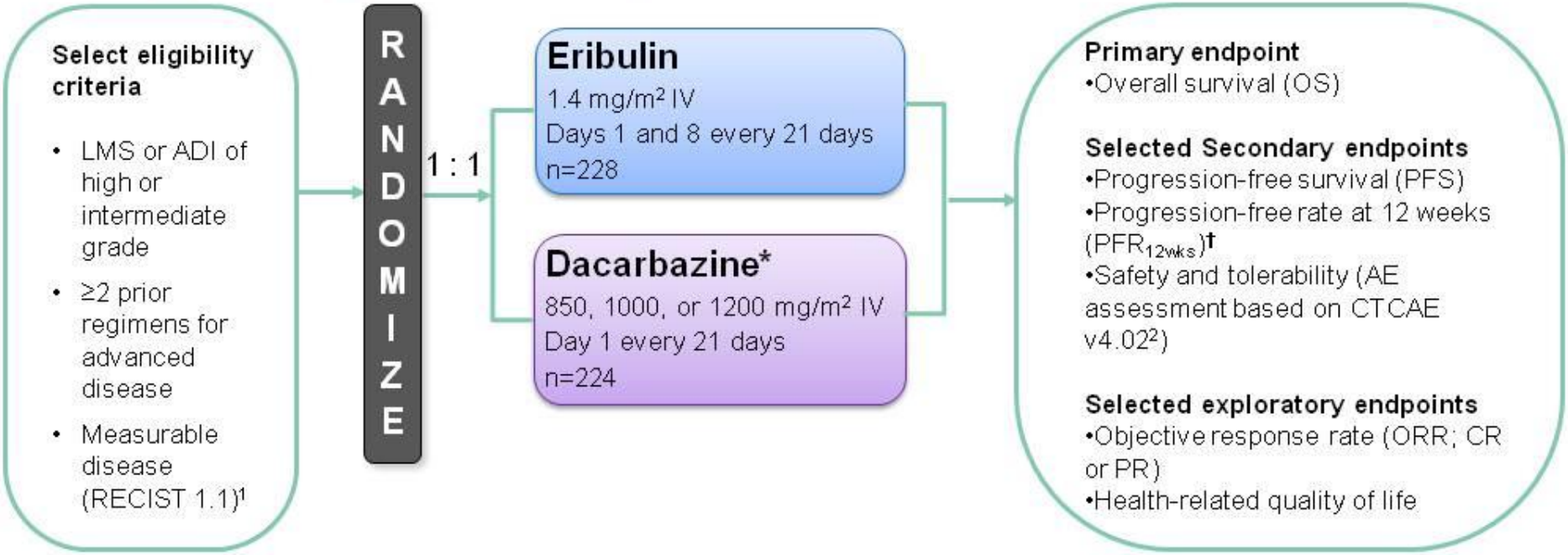
Eribulin binds specifically to (+) ends of microtubules, inhibiting only the growth phase of microtubule dynamics[2,3]

EU, European Union; USA, United States of America.

1. Towle et al. *Cancer Res* 2001; 2. Jordan et al. *Mol Cancer Ther* 2005; 3. Smith et al. *Biochemistry* 2010; 4. Halaven EPAR; 5. Halaven prescribing information; 6. Funahashi et al. *Cancer Sci* 2014; 7. Yoshida et al. *Br J Cancer* 2014. *Halichondria okadai* image (*top left*) © 2015 – Reproduced with the kind permission of G. & P. Poppe; microtubule image (*right*) adapted, with permission, from Macmillan Publishers Ltd: *Nat Rev Cancer* 2004;4:253–65, ©2004.

Presented By Patrick Schoffski at 2015 ASCO Annual Meeting

Study design and objectives



*Starting dose selected by the local investigator at study initiation; †PFR_{12wks}, proportion of patients who were still alive without disease progression at 12 weeks from randomization.

CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenous; OS, overall survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Eisenhauer et al. *Eur J Cancer* 2009; 2. CTCAE v4.02 available at http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf; accessed May 6, 2015.

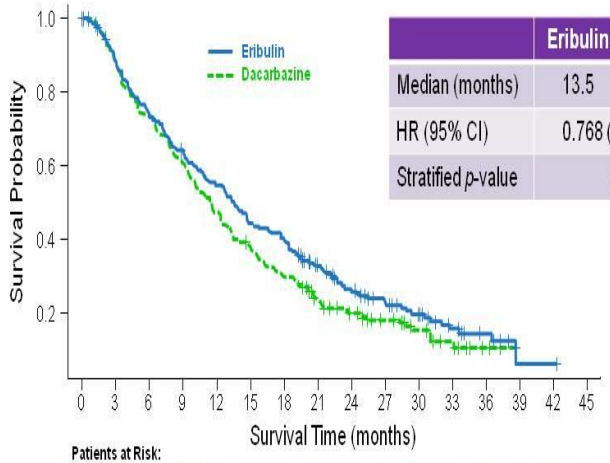
Key patient characteristics (continued)

Category	Subgroup	Eribulin (n=228) n (%)	Dacarbazine (n=224) n (%)
Histology	ADI LMS Other	75 (32.9) 152 (66.7) 1 (0.4)	78 (34.8) 145 (64.7) 1 (0.4)
ADI histological subtype	Dedifferentiated Myxoid/Round cell Pleomorphic	32 (14.0) 30 (13.2) 13 (5.7)	37 (16.5) 26 (11.6) 15 (6.7)
LMS primary site	Uterine Nonuterine	67 (29.4) 85 (37.3)	62 (27.7) 83 (37.1)
Tumor grade	High Intermediate Not done	150 (65.8) 77 (33.8) 1 (0.4)	152 (67.9) 69 (30.8) 3 (1.3)
Number of prior regimens for advanced disease	0 1 2 >2	1 (0.4) 15 (6.6) 116 (50.9) 96 (42.1)	1 (0.4) 14 (6.3) 98 (43.8) 111 (49.6)

→ Eribulin mit OS-Vorteil +2 Monate bei L-Sarkomen

→ starker Effekt bei Liposarkomen

Primary endpoint: OS



	Eribulin	Dacarbazine
Median (months)	13.5	11.5
HR (95% CI)	0.768 (0.618, 0.954)	
Stratified *p*-value	0.0169	

Patients at Risk:

Eribulin	228	197	162	138	120	97	88	64	45	34	25	14	7	1	1	0
Dacarbazine	224	190	158	130	103	81	64	45	32	24	16	8	3	0	0	0

- The primary endpoint of OS was met, indicating a 2-month improvement in median OS with eribulin

CI, confidence interval.

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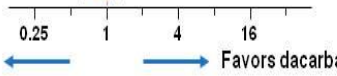
Preplanned OS subgroups analysis (continued)

Group/Subgroup	Events/n — Eribulin	Events/n — Dacarbazine	HR (95% CI)	Median (months) — Eribulin	Median (months) — Dacarbazine
Histology					
ADI	52/71	63/72	0.511 (0.346, 0.753)	15.6	8.4
LMS	124/157	118/152	0.927 (0.714, 1.203)	12.7	13
AJCC sarcoma tumor grade score at the date of diagnosis					
High	118/150	125/152	0.796 (0.607, 1.042)	12.7	11.5
Intermediate	57/77	55/69	0.649 (0.439, 0.961)	14.8	10.1
Baseline ECOG PS					
0	76/111	72/90	0.579 (0.407, 0.823)	19.9	13.1
1	97/114	97/121	1.107 (0.826, 1.484)	9.4	10.1
2	3/3	12/13	3.000 (0.251, 35.794)	1.1	3
Prior anticancer therapy type					
Anthracycline	174/225	177/219	0.770 (0.619, 0.958)	13.5	11.3
Gemcitabine	101/129	111/138	0.803 (0.600, 1.074)	13.2	11.8
Ifosfamide	108/141	115/137	0.701 (0.529, 0.930)	14.7	11
Taxane	87/109	92/114	0.835 (0.604, 1.156)	11.3	11.6
Trabectedine	80/108	98/116	0.643 (0.469, 0.884)	13.3	10.7
Targeted therapy	23/29	19/26	1.067 (0.527, 2.161)	11.3	13.1
Other	66/83	70/90	0.902 (0.631, 1.289)	11.3	12.2



AJCC, American Joint Committee on Cancer.

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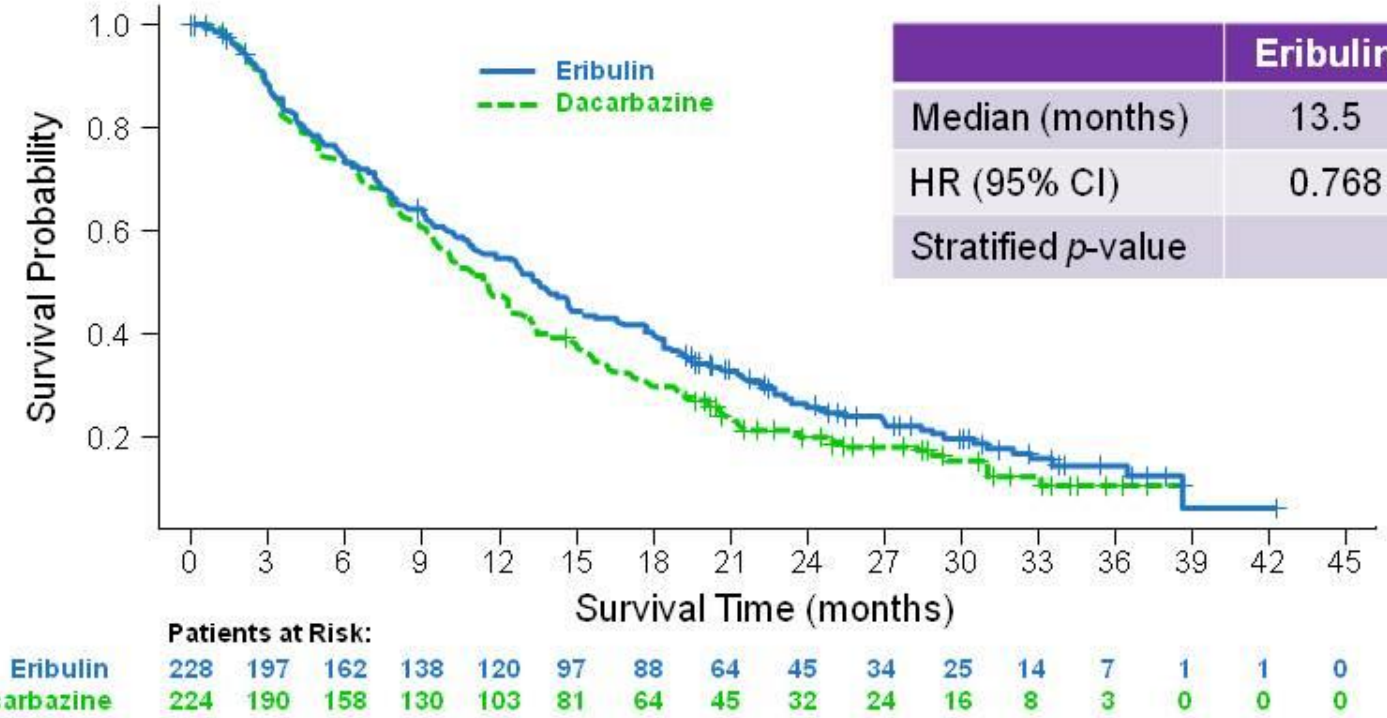
modifiziert, Presented By Patrick Schoffski at 2015 ASCO Annual Meeting

Primary endpoint: OS



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- The primary endpoint of OS was met, indicating a 2-month improvement in median OS with eribulin

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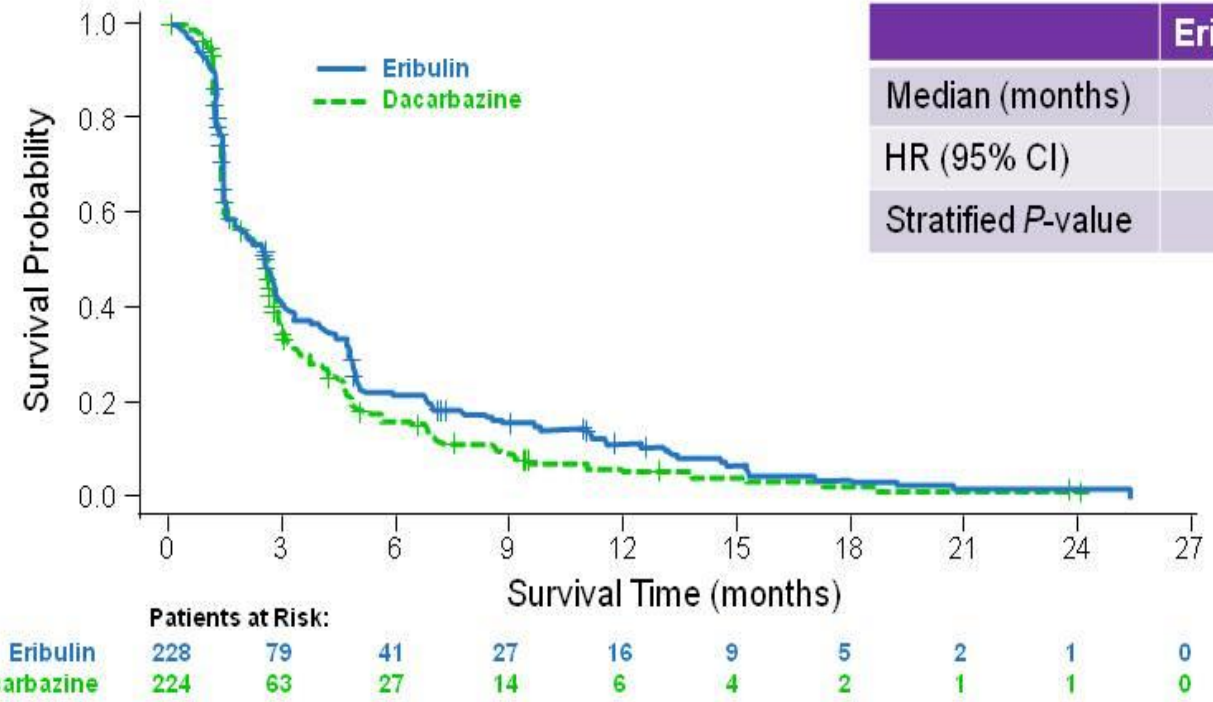
Secondary endpoint: PFS



	Eribulin	Dacarbazine
Median (months)	2.6	2.6
HR (95% CI)	0.877 (0.710, 1.085)	
Stratified *P*-value	0.2287	

Preplanned OS subgroups analysis (continued)

Group/Subgroup	Events/n — Eribulin	Events/n — Dacarbazine	HR (95% CI)	Median (months) — Eribulin	Median (months) — Dacarbazine
Histology					
ADI	52/71	63/72	0.511 (0.346, 0.753)	15.6	8.4
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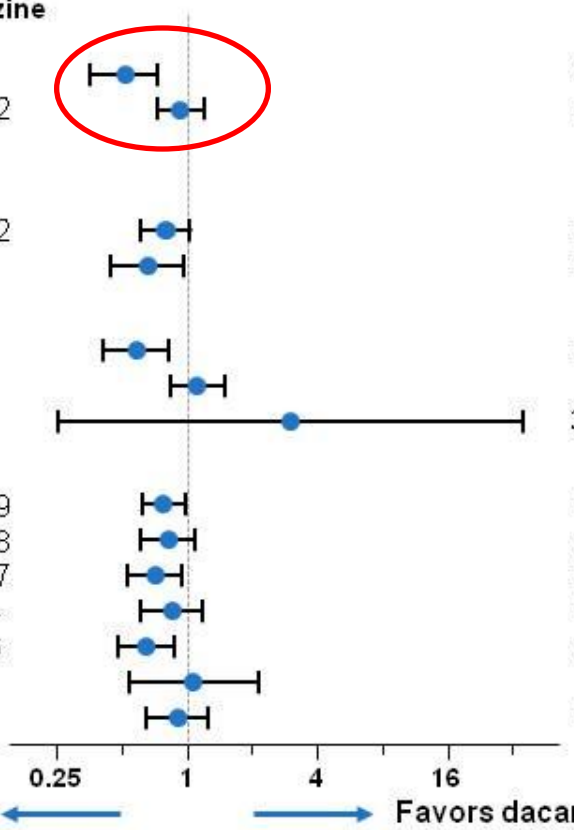

AJCC, American Joint Committee on Cancer.

Most frequent AEs ≥20% patients across all treatment cycles, per patient

	Eribulin (n=226) n (%)		Dacarbazine (n=224) n (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Patients with any AEs	224 (99.1)	152 (67.3)	218 (97.3)	126 (56.3)
Neutropenia	99 (43.8)	80 (35.4)	53 (23.7)	35 (15.6)
Fatigue	99 (43.8)	7 (3.1)	86 (38.4)	3 (1.3)
Nausea	91 (40.3)	2 (0.9)	106 (47.3)	1 (0.4)
Alopecia	79 (35.0)	–	6 (2.7)	–
Constipation	71 (31.4)	2 (0.9)	58 (25.9)	1 (0.4)
Anemia	67 (29.6)	16 (7.1)	69 (30.8)	27 (12.1)
Pyrexia	63 (27.9)	2 (0.9)	31 (13.8)	1 (0.4)
Asthenia	47 (20.8)	4 (1.8)	51 (22.8)	7 (3.1)
Peripheral sensory neuropathy	46 (20.4)	4 (1.8)	8 (3.6)	–
Thrombocytopenia	13 (5.8)	1 (0.4)	62 (27.7)	34 (15.2)

LBA10502: Randomized, open-label, multicenter, phase III study of eribulin versus dacarbazine in patients (pts) with leiomyosarcoma (LMS) and adipocytic sarcoma (ADI) - Patrick Schöffski et al

Zusammenfassung

- Primärer Endpunkt OS-Vorteil erreicht;
  - +2 Monate (HR 0,77)
  - Stärkerer Effekt bei Liposarkomen
- Kein Vorteil für Ansprechrate u. PFS, hoher Anteil an SD
- etwas erhöhte Toxizität von Eribulin

Fazit:

Erweiterung des Armentariums bei L-Sarkomen, Lipo > LMS; Zulassung, wann?

A Randomized Phase 1b/2 Study Evaluating the Safety and Efficacy of Olaratumab (IMC-3G3), a Human Anti–platelet-derived Growth Factor α (PDGFRα) Monoclonal Antibody, with or without Doxorubicin (Dox), in Advanced Soft Tissue Sarcoma (STS)

William D. Tap*

Robin L. Jones, Bartosz Chmielowski, Anthony D. Elias, Douglas Adkins, Brian A. Van Tine, Mark Agulnik, Matthew Cooney, Michael B. Livingston, Gregory Pennock, Amy Qin, Ashwin Shahir, Robert Ilaria Jr, Ilaria Conti, Jan Cosaert, Gary K. Schwartz

**Presenting Author*

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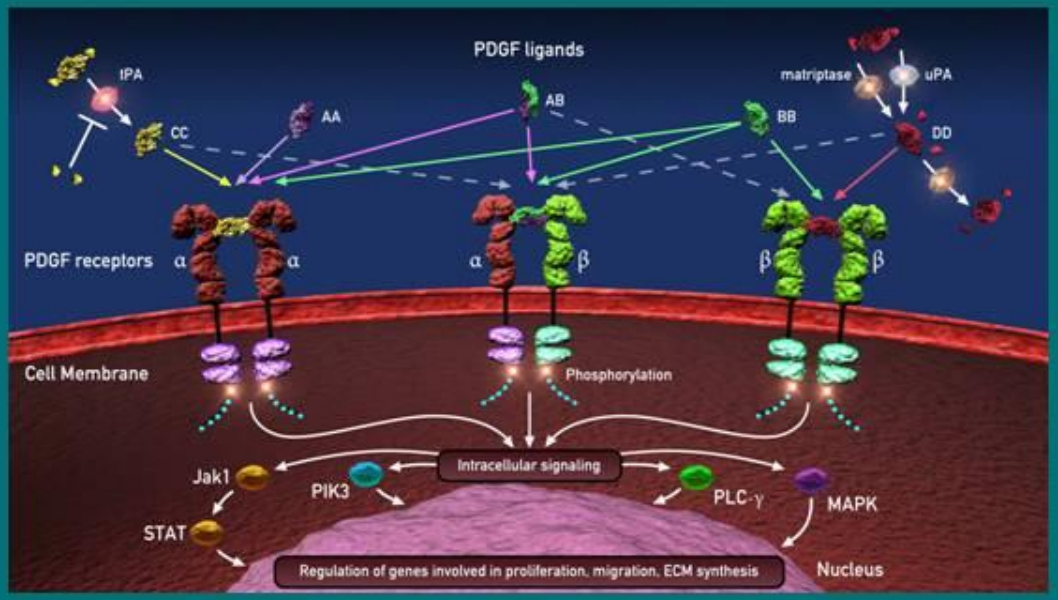
Platelet-Derived Growth Factor Receptor (PDGFR)

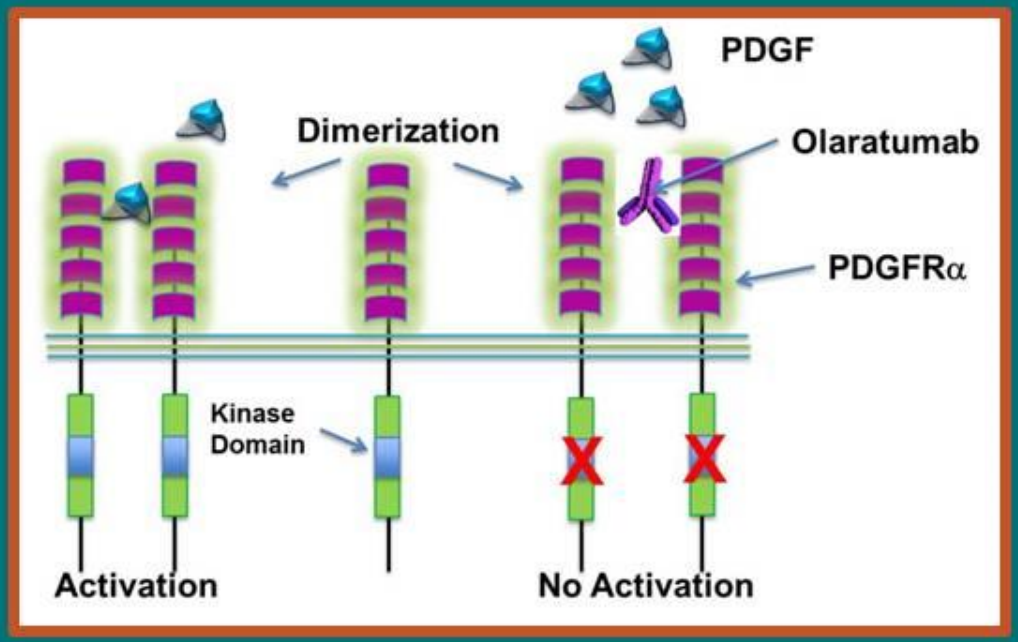
- Cell surface receptor tyrosine kinase (α,β) activated by the platelet-derived growth factor (PDGF A–D) family of ligands
- In normal mesenchymal biology, PDGF/PDGFR signaling has a significant role in the following[1-3]:
  - Mesenchymal stem cell differentiation
  - Growth of mesenchymal cells
  - Angiogenesis and wound healing



[1] Ng et al. *Blood* 2008;112(2):295-307; [2] Li et al. *PLoS One* 2014 Dec 3;9(12):e113785; [3] Andrae et al. *Genes Dev* 2008;22:1276-1312.

Olaratumab

- Fully human monoclonal antibody of immunoglobulin G class 1 (IgG1) that selectively binds PDGFRα[1]
- Blocks PDGF binding and PDGF-induced PDGFRα activation[1]
- Demonstrated activity in both in vitro and in vivo cancer models known to be driven by a PDGF-PDGFRα autocrine loop[2,3]
- Demonstrated antitumor activity alone[1] or in combination with Dox in human sarcoma xenograft models[4]



[1]Loizos et al. *Mol Cancer Ther* 2005;4(3):369-79 ; [2] Gerber et al. *Mol Cancer Ther* 2012;11(11):2473-82; [3,4]Data on file, Eli Lilly and Company

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Open-label, Multicenter, Phase 1b/2 Trial

Phase 2

- Same entry criteria as Phase 1b
- Stratification:
  - PDGFRα (IHC)
  - Lines of prior treatment
  - ECOG PS
  - Histology (leiomyosarcoma, synovial sarcoma, other)

RANDOMIZE

- Olaratumab 15 mg/kg D1,8 + Dox 75 mg/m^2 D1 × 8 cycles (21 days)* → Olaratumab monotherapy until progression
- Dox 75 mg/m^2 D1 × 8 cycles → Optional olaratumab monotherapy after progression

Primary endpoint: Progression-free survival (PFS) (predefined statistical significance: 2-sided alpha = 0.2)

Secondary end points: Overall survival (OS), objective response rate, PFS at 3 months

Biomarker: PDGFRα (IHC) and related ligands

* During Cycles 5-8, patients receiving Dox could receive dexrazoxane, at the investigator's discretion.

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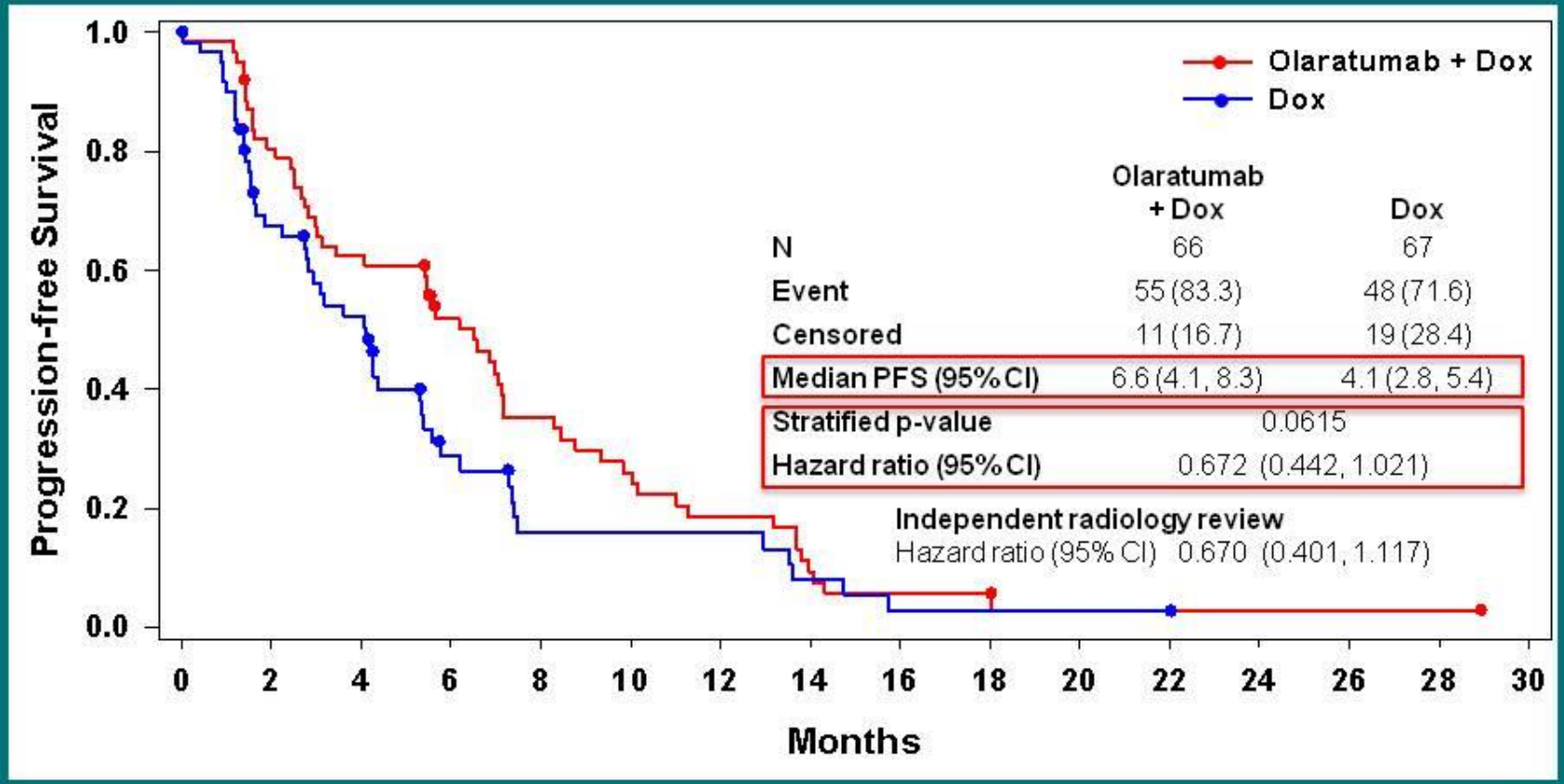
Histological Subtypes

Histological Subtype	Olaratumab + Dox (N=66)	Dox (N=67)
Angiosarcoma	4 (6.1)	3 (4.5)
Fibrosarcoma	1 (1.5)	0
Leiomyosarcoma	24 (36.4)	26 (38.8)
Liposarcoma	8 (12.1)	15 (22.4)
Neurofibrosarcoma	1 (1.5)	0
Pleomorphic sarcoma	11 (16.7)	14 (20.9)
Synovial sarcoma	1 (1.5)	2 (3.0)
Other	16 (24.2)	7 (10.4)

- Leiomyosarcoma was the most common histological subtype, representing slightly more 1/3 patients in each arm

Progression-Free Survival (ITT) (Phase 2)



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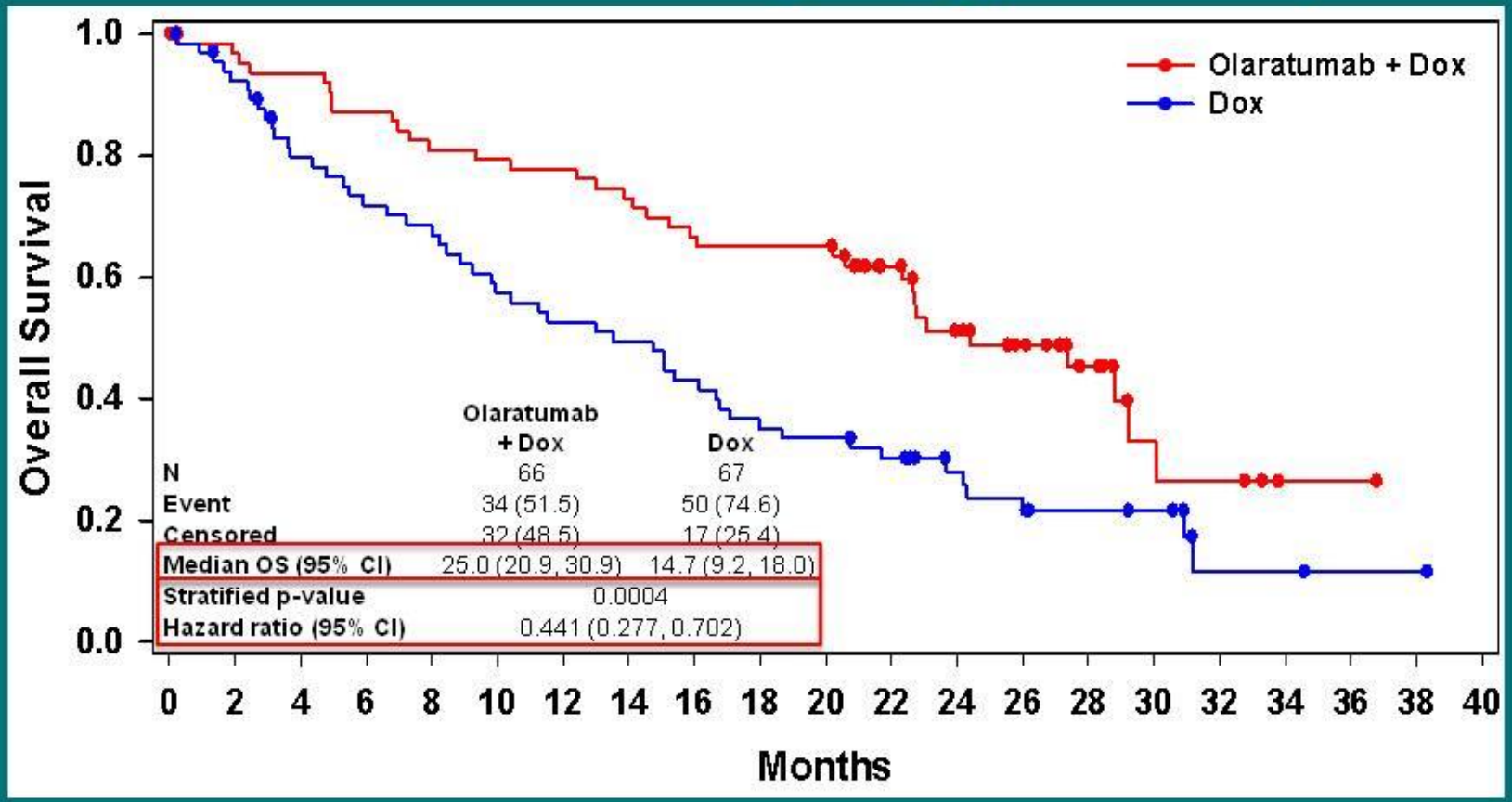
Overall Survival (ITT) (Phase 2)



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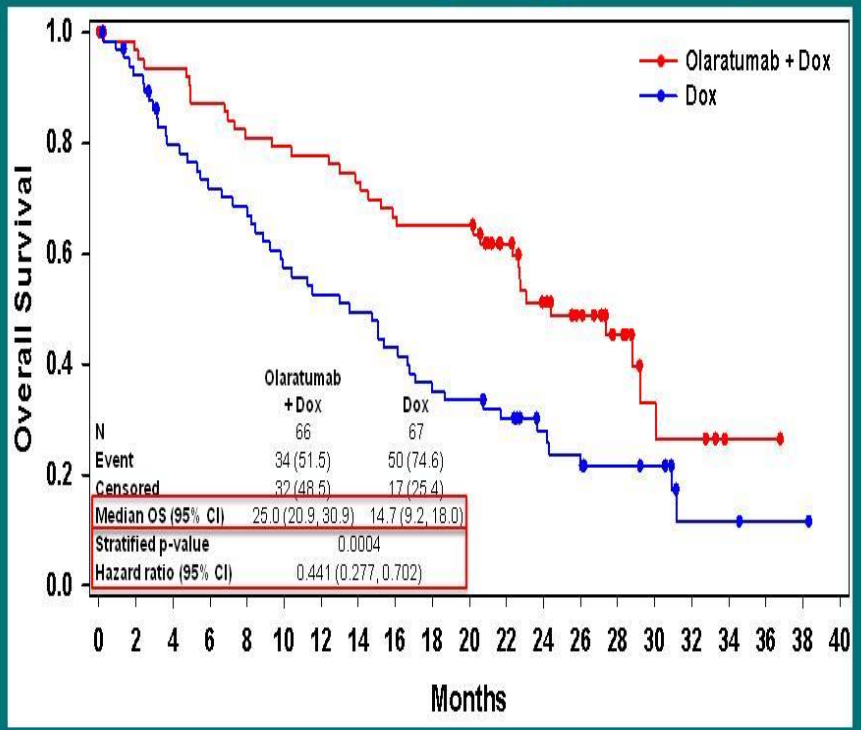
→ Olaratumab Verbesserung *OS* um +10 Monate

Overall Survival (ITT) (Phase 2)



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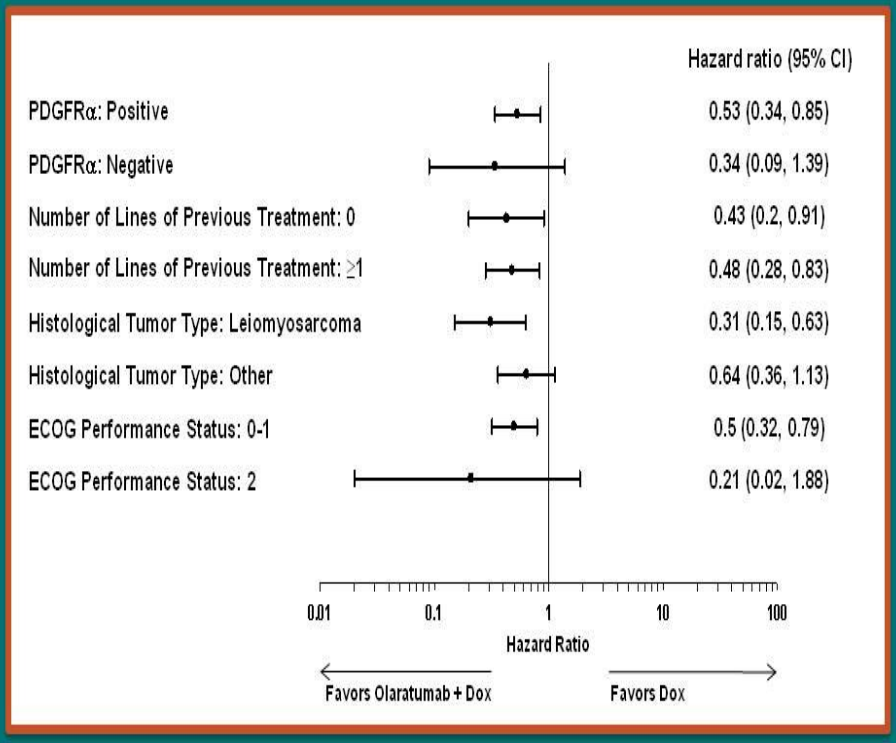
Overall Survival (ITT) by Stratification Factor (Phase 2)



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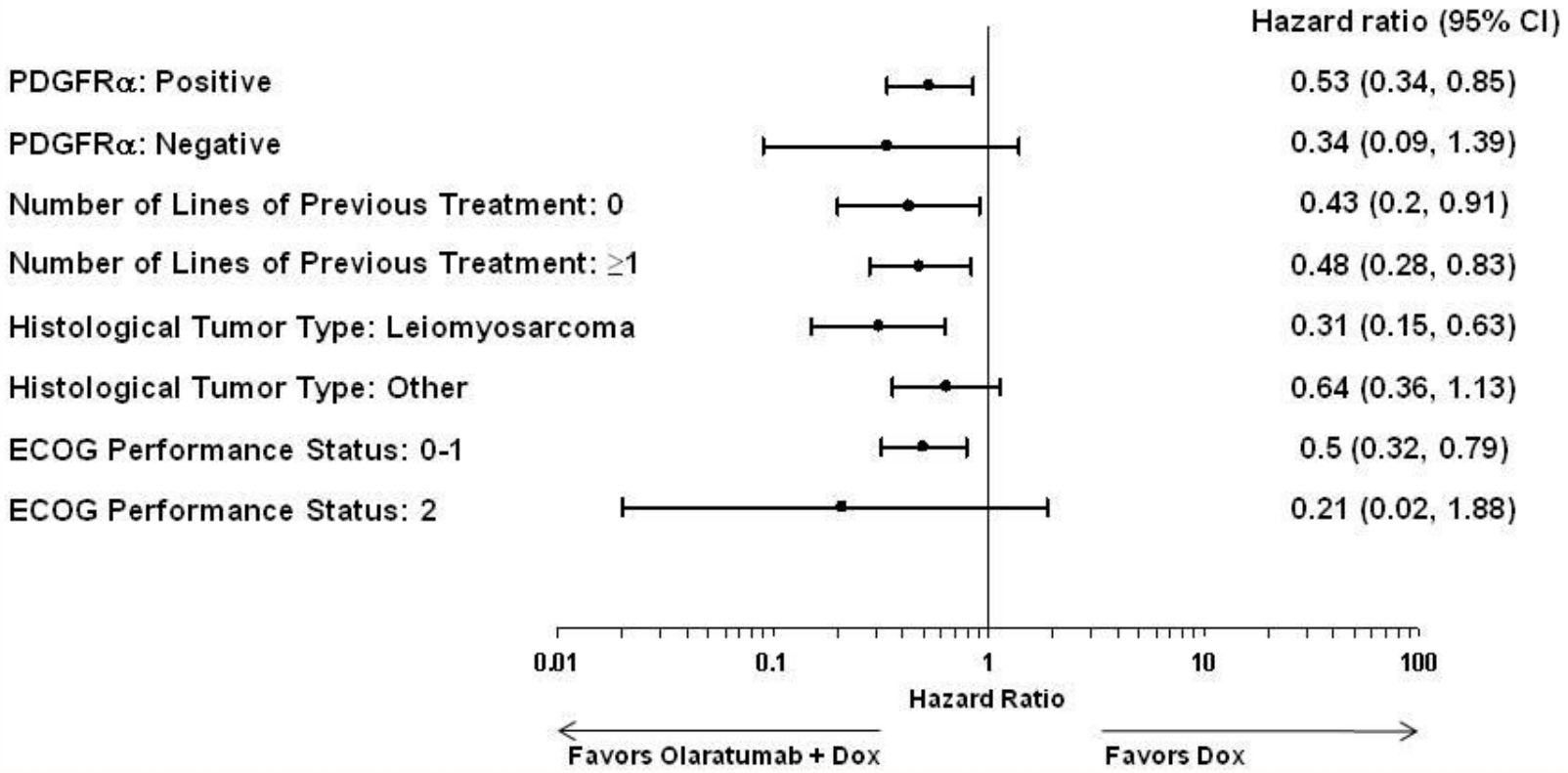
Overall Survival (ITT) by Stratification Factor (Phase 2)



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Grade ≥3 Adverse Events that Occurred in ≥ 5% of the population (Phase 2)

Adverse event, no. pts (%)	Olaratumab + Dox (N=64)	Dox (N=65)
Neutropenia	33 (51.5)	22 (33.8)
Anemia	8 (12.5)	5 (7.7)
Febrile neutropenia	8 (12.5)	9 (13.8)
Fatigue	6 (9.4)	2 (3.1)
Thrombocytopenia	6 (9.4)	5 (7.7)
Infections	4 (6.3)	7 (10.8)

- Neutropenia did not translate into higher rates of febrile events or infections

Cardiac Adverse Events and Changes in Function (Phase 2)

- Overall incidence of any cardiac adverse event
  - 14.1% (olaratumab + Dox) vs 9.2% (Dox)
- Ejection fraction decreased
  - 4.7% (olaratumab + Dox) vs 6.2% (Dox)
- Changes in LVEF function
  - LVEF <50% at any time during study*
    - 11.8% (olaratumab + Dox) vs 9.4% (Dox)

Median cumulative Dox dose:
- 525 mg/m^2 (olaratumab + Dox)
- 300 mg/m^2 (Dox)

*Of patients with a baseline assessment and at least 1 post-baseline assessment

AE = adverse event; LVEF = left ventricular ejection fraction

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10501: A randomized phase Ib/II study evaluating the safety and efficacy of olaratumab (IMC-3G3), a human anti-platelet-derived growth factor α (PDGFRα) monoclonal antibody, with or without doxorubicin (Dox), in advanced soft tissue sarcoma (STS). – William D. Tap et al

Zusammenfassung

- Doxo+Olaratumab Verbesserung medianes *OS* um 10,3 Monate
- Kombination mit akzeptabler Toxizität (auch nicht signifikant mehr Kardiotox.)

Fazit:

Vielversprechende Daten

Phase III folgt

“Breakthrough Therapy Designation” der FDA

Immuntherapien bei Sarkomen

TPS10578: SARC 028: A phase II study of the anti-PD1 antibody pembrolizumab (P) in patients (Pts) with advanced sarcomas. Melissa Amber Burgess et al

- Prästudien:
  - Bis zu 65 % von 150 Sarkompats versch. Histologien expremierten PD1 und PD1+ tumorinfiltrierenden Lymphozyten
  - → Korrelation mit aggressiverem Verlauf und schlechterem OS

→ Studie: 2 Arme (WTS und Knochens.) je 40 pts
10 Zentren; 200 mg Pembrolizumab alle 3 Wo
Endpunkte ORR, PFS; Rekrutierungsende 2015

CTx Weichteilsarkome - Agenda

Allgemeines

Therapie palliativ

Ausblick palliative Therapie

- Therapie neoadjuvant/adjuvant

WTS adjuvante CTx

clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii102–iii112, 2014
doi:10.1093/annonc/mdu254

Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

The ESMO/European Sarcoma Network Working Group*

Kein Konsens zur Rolle adjuvanter CTx

- größere Studien negativ Woll PJ et al. EORTC 6293; Lancet Oncol 2012; 13: 1045–1054.
- kleinere Studien mit teils OS Benefit Frustaci S et al. J Clin Oncol 2001; 19: 1238–1247.
- Metaanalyse mit OS+RFS-Benefit Pervaiz et al. Cancer 2008; 113: 573–581.

→Option für Hoch-Risiko-Patienten (high-grade, tief, Tm > 5 cm), "shared decision-making"

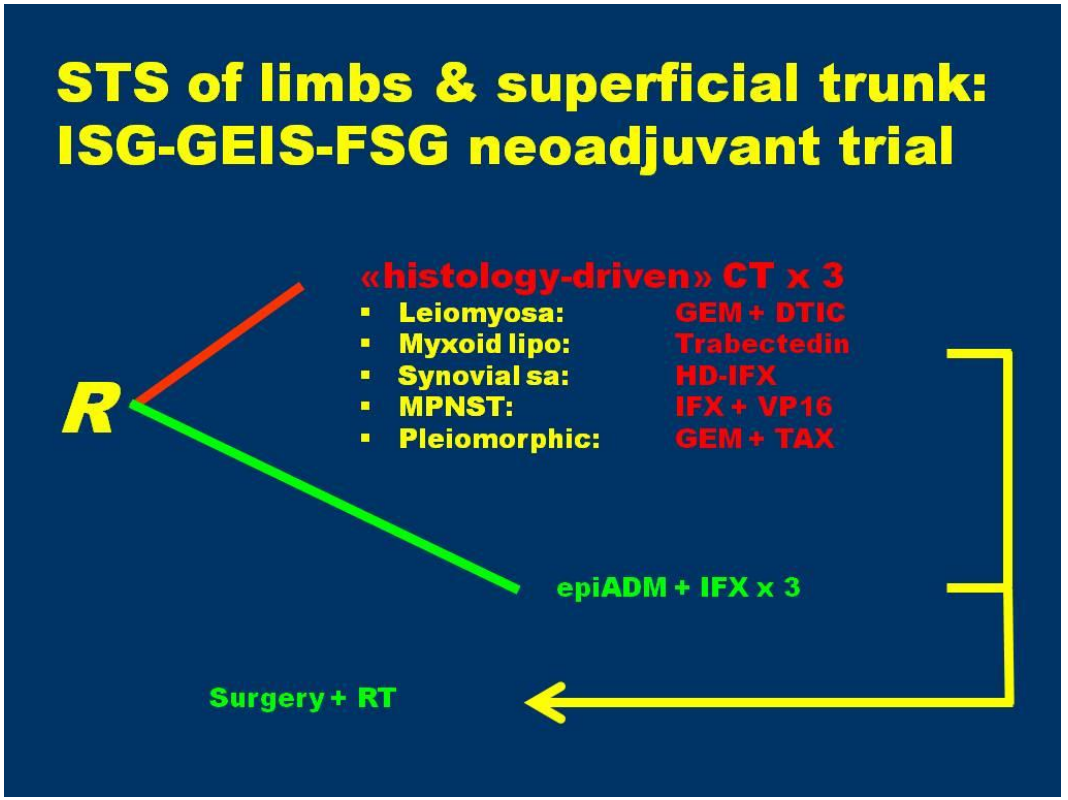
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Aktuelle Publikation:

Feasibility of Preoperative Chemotherapy With or Without Radiation Therapy in Localized Soft Tissue Sarcomas of Limbs and Superficial Trunk in the Italian Sarcoma Group/ Grupo Español de Investigación en Sarcomas Randomized Clinical Trial: Three Versus Five Cycles of Full-Dose Epirubicin Plus Ifosfamide

Elena Palassini, Stefano Ferrari, Paolo Verderio, Antonino De Paoli, Javier Martin Broto, Vittorio Quagliuolo, Alessandro Comandone, Claudia Sangalli, Emanuela Palmerini, Antonio Lopez-Pousa, Rita De Sanctis, Stefano Bertelli, Michela Libertini, Piero Picci, Paolo G. Casali, and Alessandro Gronchi

Phase III Studie (laufend, NCT01710176):



CTx WTS - Zusammenfassung

Erstlinie: Doxorubicin mono
individuell Kombi mit Ifosfamid

Zweitlinie: Subgruppenspezifische Therapie
neue Substanzen Eribulin?, Olaratumab?

Adjuvant/neoadj.: keine generelle Empfehlung
weitere Studien ausstehend

clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii102–iii112, 2014
doi:10.1093/annonc/mdu254

Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

The ESMO/European Sarcoma Network Working Group*

There is no consensus on the current role of adjuvant chemotherapy.
Study results are conflicting, in the presence of negative results from the largest studies, though data are available from smaller studies suggesting that it might improve, or at least delay, distant and local recurrence in high-risk patients [13, 14].
A meta-analysis found a statistically significant limited benefit in terms of both survival- and relapse-free survival [15]. It is unknown whether adjuvant chemotherapy may be particularly beneficial in specific subgroups or even detrimental in others. Therefore, adjuvant chemotherapy is not standard treatment in adult-type STS. It can be proposed as an option to the high-risk
individual patient (high-grade, deep, >5 cm tumour) for a shared decision-making with the patient [II, C] or within…

WTS – Take Home Message

The GOOD OLD:

- 1st line: Doxo mono weiter Standard, Gem/Doce gleichwertig (?)
- 2nd line: Trabectedin bestätigt PFS-Vorteil, mit Langzeitansprechern; Einsatz Erhaltung, Neoadj.? (laufende Studien)

WTS – Take Home Message

- The NEW:
  - Eribulin mit OS-Vorteil, Zulassung wann?
  - Olaratumab/Doxo OS-Vorteil vielversprechende Daten, Phase III ?
  - 2nd line: Regorafenib, OS-Vorteil bei LMS, Phase III ?
- Ausblick

  Immuntherapien, laufende Phase II


Vielen Dank
für Ihre
Aufmerksamkeit!